REMARKS

The Applicants hereby submit an Information Disclosure Statement, Form PTO-1449, to comply with 37 CFR § 1.98(a)(1) listing the references already of record in the instant Specification and/or the International Search Report which was transmitted to the Office by the International Bureau and/or which have otherwise been brought to the attention of the applicant. As will be noted, this Information Disclosure Statement calls a number of references, which might be considered relevant, to the attention of the Office. The fact that these are in fact "prior art" and/or relevant to the prosecution is, however, not admitted. It is understood that, during examination, the Office will make an independent search and will identify any relevant prior art under 37 CFR § 1.104(a).

The Applicants acknowledge the Non-Final Office Action of January 25, 2005 with appreciation as well as the graciously granted Examiner's Interview of July 18, 2005. The Office indicates Claims 11-15 are pending in the application. The Applicants enquire as to the status of Claims 16-18 in the present application. A Supplemental Response and Amendment under 37 CFR §§ 1.111 and 1.115 was filed October 28, 2004 to bring to the Office attention an error in the enumeration in pending claims, specifically the status of claims 16-18. Although the Response is acknowledged in the instant Office Action, the Office fails to indicate the status of Claims 16-18 in the instant Office Action Summary. The Applicants request that the Office acknowledge the pendency of all of the Claims 11-18.

The Office maintains the rejection of all claims for obviousness under 35 U.S.C. § 103(a) based upon the disclosure of several prior art references. The Examiner designates Göschel, et al., (Experimental Neurology 1997, 147:96-102) as the primary reference for combination with other references to formulate the obviousness rejections.

In the Response and Amendment of August 27, 2004, the Applicants rebutted the Office basis for the obviousness rejection on the premise that the cited prior art do not suggest all claim limitations, particularly a *Clostridium botulinum* neurotoxin which is free of complexing proteins which naturally form complexes with botulinum neurotoxins for the treatment of subjects already exhibiting neutralizing antibodies to neurotoxin complexes.

The Office maintains the rejections under 35 U.S.C. § 103(a) over Göschel, et al. on the basis of selected disclosure statements, specifically that Göschel, et al. make the suggestion that "botulinum toxin preparations should be purified from concomitant proteins, thereby reducing the load of foreign substances that might lead to untoward reactions (page 102)." To make out a *prima facie* rejection for obviousness, the Office concludes that the quoted statement provides the requisite teaching to meet all claim limitations when combined with the teaching of the cited prior art. Although Göschel, et al. may teach or suggest purification of botulinum toxins from concomitant proteins to satisfy a claim limitation, to make out a *prima facie* rejection for obviousness the Office must further identify some teaching, suggestion, or motivation to combine the teaching of the prior art, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, and to make out a rejection encompassing the claimed methods, because the instant claims are directed to methods, not compositions.

Considering the context of the entire passage from which the quoted statement of Göschel, et al. is derived, the specific disclosure language pertains to botulinum toxins free from concomitant proteins for the reduction of antigenicity. The quoted statement in Göschel, et al. makes the "suggestion" that the toxin should be purified from concomitant proteins to reduce the load of foreign substances that might lead to untoward reactions. The Office admits that, "In this case, Göschel, et al. makes the suggestion that botulinum toxin preparations should be purified from concomitant proteins, thereby reducing the load of foreign substances that might lead to untoward reactions (page 102)." throughout the instant Office Action. The Applicants submit that "untoward reaction" is a term used by those skilled in the art to describe an undesired effect and Göschel, et al. provide an example of an

untoward reaction by disclosing "a case of rash linked to Dysport administration" (page 102). Therefore, the Göschel, et al. disclosure of purification from concomitant proteins is directed to preventing adverse immunological reactions, such as rash. This is not unlike the Göschel, et al. disclosure that the concomitant proteins might serve as adjuvants that stimulate the production of anti-neurotoxin antibodies (page 102). Consequently, Göschel, et al. may be cited for the disclosure of purifying botulinum neurotoxin preparations from concomitant proteins for the reduction of antigen load. This teaching does not, however, extend to the surprising discovery that a botulinum neurotoxin preparation free from complexing proteins will be effective in treating subjects already exhibiting neutralizing antibodies, which is the subject of the instant invention.

In fact, the reference disclosure teaches that subjects who have developed neutralizing antibodies would not benefit from treatment with botulinum neurotoxins. Göschel, et al. state that, "Neutralizing antibodies, as the cause of therapeutic failure, were also identified with the help of the mouse *in vivo* toxin neutralization assay." (page 101). Göschel, et al. disclose that neutralizing antibodies were exclusively directed against the neurotoxic constituent of the complex (page 99, last paragraph). Therefore, Göschel, et al., teach that a botulinum toxin free from complexing proteins and comprising only the neurotoxic constituent would not be effective in subjects already exhibiting neutralizing antibodies. In view of the entire disclosure of Göschel, et al., the Applicants submit that one skilled in the art would not be motivated to administer a botulinum neurotoxin, which is free from complexing proteins, to treat subjects already exhibiting neutralizing antibodies.

The Applicants, herewith, submit references which are listed with the Information Disclosure Statement. Generally, the disclosure pertains to the problem of neutralizing antibodies as the cause of therapeutic failure and to the antigenicity of neurotoxin complexes. The Applicants invite the Office to consider the disclosure of Aoki, KR (European Journal of Neurology, 1999, 6 (suppl 4):S3-S10) which is representative of the state of the art at the time of the invention with regard to the clinical application of *Clostridium botulinum* toxin preparations. Aoki compares the efficacy of botulinum toxin preparations, including free neurotoxin. The Applicants

direct the Office attention to Figure 4 which graphically demonstrates that Type A free neurotoxin is inferior to Type A neurotoxin complexes in muscle weakening efficacy. Aoki discloses on page S5, second full paragraph, that the haemagglutinins are considered to provide a stabilizing effect on neurotoxin, and therefore, contribute to efficacy by preventing diffusion. Aoki discloses on page S8 that, "It is also possible that neurotoxin complex size may play a role if the presence or absence of the associated non-toxin proteins (such as the haemagglutinins) affect toxin stability following injection and/or the tendency to diffuse away from the target muscle." Consequently, those skilled in the art at the time of the invention considered botulinum neurotoxin complexes to provide greater efficacy in patients.

Moreover, the Applicants submit that the instant invention is not meant to be considered and may not be characterized as simply substituting an alternate toxin serotype in a subject who has developed neutralizing antibodies to one serotype. With respect to the use of alternative botulinum neurotoxin serotypes, the Applicants refer to the previously discussed Aoki, KR (European Journal of Neurology, 1999, 6 (suppl 4):S3-S10) disclosure. The reference discloses cross-reactivity of neutralizing antibodies between toxin serotypes (Table 1, page S7, at right column) which was understood by those skilled in the art at the time of the instant invention. Consequently, it may not be stated that those skilled in the art would be motivated to substitute toxin types to treat patients already exhibiting neutralizing antibodies with a reasonable expectation of success. Rather, the instant invention pertains to the discover that the instant preparations, free of complexing proteins, are suitable for administration to patients already exhibiting neurotoxin antibodies, without respect to serotype.

To address the individual rejections, Claims 11 and 12 are rejected under 35 U.S.C. §103(a) as being obvious over Göschel, et al., (Experimental Neurology 1997, 147:96-102) in view of Borodic, et al., (Ophthalmic Plastic and Reconstructive Surgery 1993, 9:182-190). The Office concludes that Göschel, et al. disclose that neutralizing antibodies were found in the sera of all non-responders (pages 98-99) and that the presence of neutralizing antibodies is the cause of therapeutic failure (page 101). The Office contends that Borodic, et al. teach the use of botulinum

neurotoxin type B for adjuvant therapy for subjects who are resistant or refractory to botulinum A toxin. The Office concludes that it would be *prima facie* obvious to combine the teaching of Göschel, et al. with the teaching of Borodic, et al. to arrive at the instant invention.

The Applicants acknowledge that Göschel, et al. teach that neutralizing antibodies are the cause of therapeutic failure. The fact that Göschel, et al. teach that neutralizing antibodies are the cause of therapeutic failure does not render the instant claims to administration of a botulinum toxin, free of complexing proteins, obvious.

Moreover, the Applicants note that Borodic, et al. do not teach or suggest administration of botulinum neurotoxins free from complexing proteins. Rather, Borodic, et al. suggest an unmodified botulinum toxin type B as a therapeutic alternative to unmodified botulinum toxin A. In view of Borodic, et al., the Applicants submit that one skilled in the art would not be motivated to administer a botulinum neurotoxin free from complexing proteins to solve the problem of therapeutic non-response because Borodic, et al. teach administration of an unmodified alternate botulinum toxin serotype as adjuvant therapy for patients resistant or refractory to botulinum A toxin. Consequently, there is no motivation or suggestion to combine the teaching of Borodic, et al. directed to an unmodified type B neurotoxin with the teaching of Göschel, et al. directed to a type A neurotoxin purified from concomitant proteins.

The Office maintains the rejection of Claims 11-13 under 35 U.S.C. 103(a) for obviousness over Göschel, et al. in view of Shelley, et al., (J Am Acad Dermatol. 1998, 28:227-9) in view of Borodic, et al. The Office concludes that Göschel, et al. teach a method of treating patients having the claimed therapeutic indications treatable with botulinum neurotoxin A and that patients develop neutralizing antibodies against botulinum toxin A. The Office views Shelley, et al. to teach a method of treating patients with hyperhidrosis using botulinum toxin A therapy. The Office cites Borodic, et al. as teaching the use of botulinum toxin B as an alternative to botulinum toxin A in patients who have developed neutralizing antibodies.

The combination of Göschel, et al., Shelley, et al. and Borodic, et al. fails because the instant invention is distinguished from Göschel, et al. and Borodic, et al. as per the previous discussion and, moreover, neither Shelley, et al. nor Göschel, et al. or Borodic, et al. disclose, or suggest, the use of a botulinum neurotoxin free from complexing proteins for the treatment of subjects already exhibiting neutralizing antibodies. The Applicants submit that the cited references lack the required suggestion or motivation to combine the reference teaching. Reconsideration and withdrawal of the rejection for obviousness is respectfully solicited.

Moving on, the Office rejects Claims 11-12 and 14-15 under 35 U.S.C. 103(a) as being obvious over Göschel, et al. in view of Keen, et al., (Plastic and Reconstructive Surgery, July 1994, 94, No. 1, pages 94-99) and further in view of Borodic, et al.

The Office concludes that Göschel, et al. teach a method of treating patients having the claimed therapeutic indications which are treatable with botulinum neurotoxin A. The Office finds Keen, et al. to teach a method of treating patients with hyperkinetic facial lines using botulinum toxin A therapy, and Borodic, et al. teach botulinum toxin B as an alternative to botulinum toxin A. The Office concludes it would be *prima facie* obvious to treat patients having the disorders disclosed in Göschel, et al. and Keen, et al. and who have developed neutralizing antibodies, with botulinum toxin B, as suggested by Borodic, et al.

The combination of Göschel, et al., Keen, et al. and Borodic, et al. does not suggest, nor make obvious the instant purified botulinum neurotoxin for the treatment of any condition in subjects already exhibiting neutralizing antibodies. The instant invention is distinguished from Göschel, et al. and Borodic, et al. as per the previous discussion. Furthermore, Keen, et al. do not disclose, or suggest administering a botulinum neurotoxin free from complexing proteins for the treatment of subjects already exhibiting neutralizing antibodies. The prior art combination lacks the suggestion that a *Clostridium botulinum* neurotoxin, which is free of complexing proteins which naturally form complexes with botulinum neurotoxins, would be

effective for the treatment of subjects already exhibiting neutralizing antibodies to neurotoxin complexes. Moreover, the Applicants submit that the requisite motivation to combine the reference teaching is absent as well. Reconsideration and withdrawal of the prior art rejection is respectfully requested.

The Office rejects Claims 11-12 under 35 U.S.C. § 103(a) as being obvious over Göschel, et al. in view of Borodic, et al. and further in view of Jankovic, et al., (The New England Journal of Medicine, April 25, 1991). The Office opines that it would be *prima facie* obvious to treat patients having the claimed indications for botulinum toxin therapy as disclosed in Göschel, et al. with botulinum toxin B as an alternative to botulinum toxin A as suggested Borodic, et al. or with other known toxin types as suggested in Jankovic, et al.

The instant invention is distinguished from Göschel, et al. and Borodic, et al. as per the previous discussion. The Applicants further submit that in view of Jankovic, et al., one skilled in the art would not be motivated to administer a botulinum neurotoxin free from complexing proteins to solve the problem of therapeutic non-response since Jankovic, et al. suggest administration of botulinum toxins which are immunologically distinct from type A. The Applicants submit that the proposed combination fails for the reasons noted above and also submit that the references lack the requisite suggestion or motivation to combine the teaching of the prior art references. Reconsideration and withdrawal of the prior art rejection is respectfully requested.

In conclusion, the non-obviousness of the instant invention resides in the discovery that patients exhibiting neutralizing antibodies to neurotoxin complexes can be effectively treated with the instant purified botulinum neurotoxins which exhibit novel performance characteristics in patients already exhibiting neutralizing botulinum neurotoxin antibodies. This surprising activity is not suggested, nor made obvious by the prior art of record. In light of these remarks, the Applicants submit the Office has not established a *prima facie* basis for rejecting the claims for obviousness.

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Accordingly, entry of the enclosed IDS, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned agent has made an earnest effort to place this application into condition for immediate allowance. If she can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call her at her below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: _____

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Enclosure: Extension Fee, three (3) months; Check in the amount of $1020.00; Information Disclosure Statement, Form PTO-1449; Accompanying References and Postal Card Receipt.

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